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Research and Technology Trends of Nutraceuticals

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1 Introduction

1-1 Needs of prophylactic medicine

In recently years, the increase of so-called life-style related diseases, such as diabetes mellitus and obesity. have been referred as social issues which leads to the loss of QOL (Quality of Life) and increases in medical care expenses. On the other hand, to positively guarantee elongation of a healthy life expectancy in an aging society is a significant social issue in Japan.

As a solution to the issue, there has been an attempt to create a society for healthy aging, by shifting the way of thinking away from life-style related diseases and "treatment by drugs" to "positive prevention of disease by food", based on the concept of "Ishoku Dogen, Healthy Eating to Prevent Disease".[1-4]

1-2 Concept of nutraceuticals

In the pharmaceutical development process, it is a requirement to have clinical test results from animal tests and studies, for verification of the effects. On the other hand, in the case of nutrition, there was no verification method for foods in preventing diseases in the past. In recent years however, as food composition has been scientifically proven to cause life style-related diseases, and has become a social issue. The concept of Nutraceuticals has started to be acknowledged as one of the measures for preventing such diseases.[2,5-10] (Figure 1)

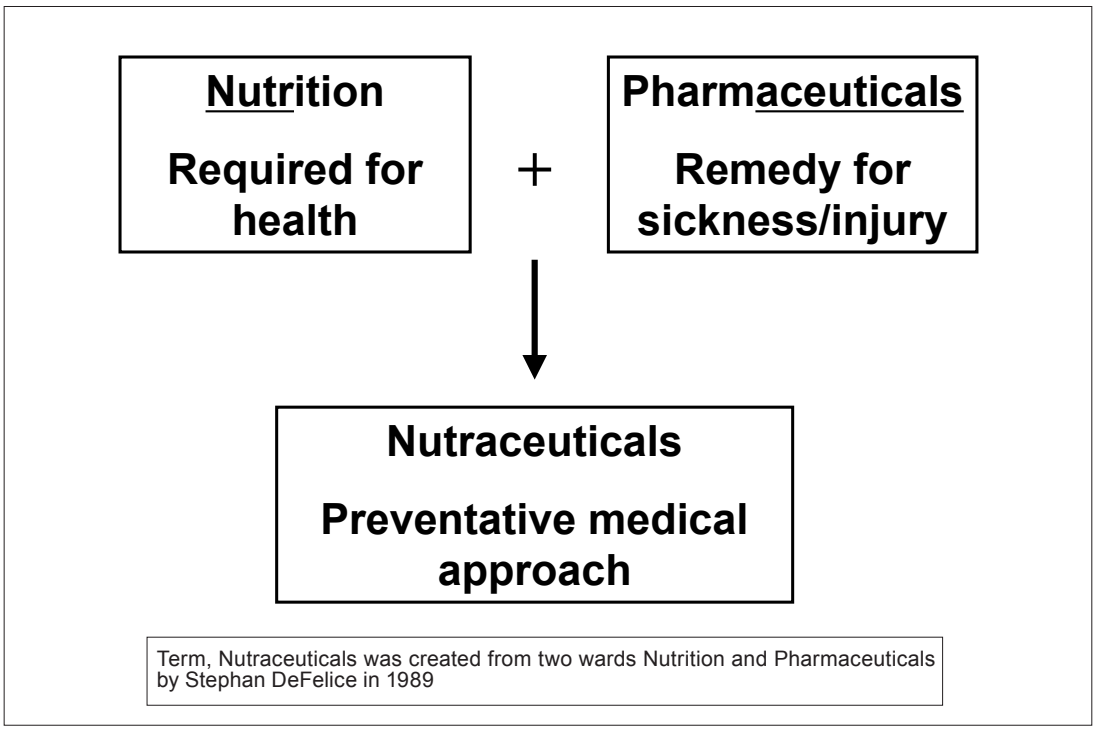

Figure 1 : Concept of nutraceuticals

Source: Reference[10]

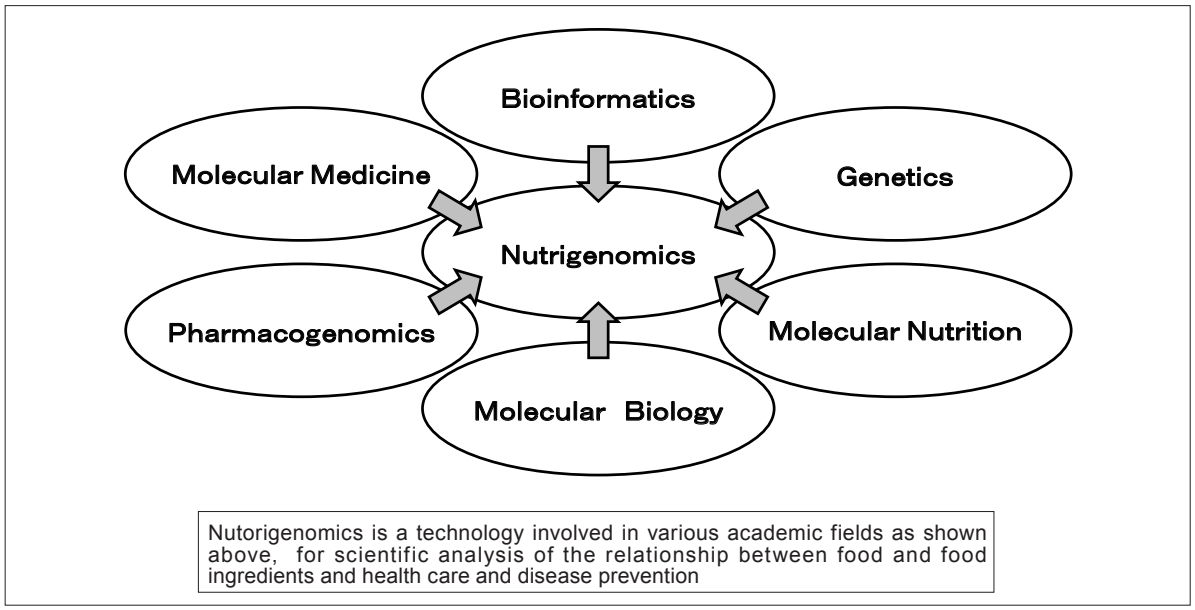

Figure 2 : Nutorigenomics technology (concept)

Prepared by the STFC based on Reference[12]

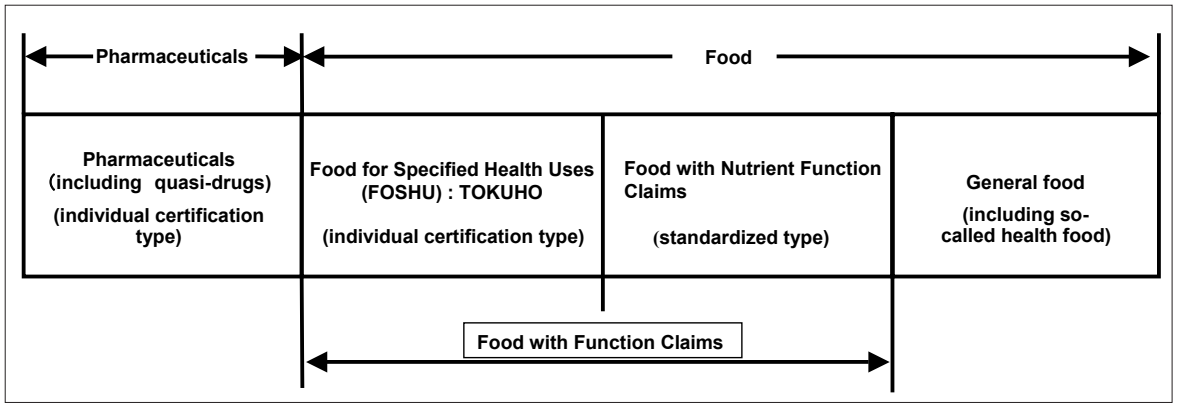

Figure 3: Function food

Source: Reference[10]

1-3 Procedure for nutrigenomics

Nutraceuticals, the new concept of food with a new function to prevent diseases, was started by the combination of genome science and technology, which has been accomplishing remarkable development for the verification. Thus, the genome technique called Nutrigenomics (nourishment genome science) was created. Nutrigenomics is newly developed methodology combined with multiple genomic techniques and molecular biology technologies, as shown in Figure 2. It has been then used as a basic technology that became a driving force for the creation of Nutraceuticals. [11-13]

In the field of the pharmaceutical development, biomarkers such as proteins levels and gene expression show the reaction to medicines, and is measured to verify the medicinal effects of drugs. Nutrigenomics technology role is to verify the medical effects of food and food composition, by linking with the biomarkers at an early stage at a level of protein and gene expression. It is now possible to determine the biomarker for each physiological function related to disease which should be prevented in order to study the mechanism for preventing the diseases, and to determine the amount of food necessary for a person to have a preventive effect towards diseases. As of now, this is only for the assessment of individual Nutraceuticals. Meanwhile, if it is possible to designate target biomarkers in order to prevent the same disease, or to standardize the assessments to have a uniform criterion, the assessment results will be further objective. It is now essential to create such a mechanism to realize this.

Furthermore, various disorders can be

predicted indivisually, including the difference of susceptibility or the difference of disease risk, and the effectiveness of drugs by analyzing the SNPs (Single Nucleotide Polymorphisms,: single nucleotide mutation), which represents personal variation of genomes. Therefore, it is thought in the future that more personalized information on food functions can be provided for disease prevention, in correspondence with individual differences of genome. Accordingly, development of the Nutrigenomics technology is expected to highly contribute to the realization of disease prevention by foods, along with Nutraceuticals, as individuals are able to obtain detailed food information effective for their health.

2 Current status of nutraceuticals in Japan

2-1 Food with function claims

In 1984, the Education Ministry (currently Ministry of Education, Culture, Sports, Science and Technology) launched the project "Systematic Analysis of Food Functions" as a special project by a Research Grant Study Group. This project is the world's first proposal of the effects of food on human bodies as a "Function",especially through the research on prevention of life-style related diseases. [2-4,13,14]

With advancement of "functional food" research, "Functional Foods (Tokutei Hoken-yo Shokuhin; "TOKUHO" in short Japanese" or Food for Specified Health Uses; FOSHU" was put into effect in 1991.

In 1993, when Shiseido marketed rice with less allergens, as the first product of TOKUHO, "Nature",world famous English academic journal, introduced in the article "Physiologically functional food" as a brand-new food concept from Japan.[15] It had a big impact and "Functional Food" was acknowledged internationally as a future food category for human health. In 2002,"standardized Food with Nutrient Function Claims;FNFC" was set up in addition to the existing FOSHU (TOKUHO) foods. FOSHU and FNFC have become the main elements in the current policy of "Food with Function Claims. (Figure 3)

FOSHU must undergo application for every individual product, and must be evaluated as effective and safe by a committee of experts, to be permitted to be displayed as "TOKUHO". The conditions for permission are the confirmed effectiveness and safety through tests of the human body and quantitative data of the functional ingredient.

Furthermore, TOKUHO was followed by "Standardized FOSHU","Disease Risk Reduction FOSHU" and "Limited Conditional FOSHU" at the time of revision in February, 2005. The concept of "Disease Risk Reduction FOSHU" is to specifically designate the foods which are medically and nutritionally proven to reduce the risk of diseases. This is one of the measures for stepping forward with disease prevention, however, there are only two kinds of elements designated in this category at the moment; calcium and folic acid."Standardized FOSHU"is the food on which has received permission, after evaluating whether the ingredients comply with the standards set by the authority. The standards are based on the pre-set standards concerning ingredients that have been proven to function by sufficient scientific reasons. There is no individual assessment of the target required. Several kinds of ingredients including dietary fiber and oligosaccharide fall into this category. In the contrast,"Limited Conditional FOSHU" is for foods permitted with the condition that it should have a label to represent the limited scientific evidence of ingredient effectiveness, even though it is insufficiently backed-up by scientific data. (Table 1)

As for FOSHU (TOKUHO), 752 items are now authorized and listed as of December 2007. This shows that TOKUHO has been penetrating the Japanese market.

Meanwhile, "FNFC" lists only five kinds of minerals and 12 kinds of nutrients. These foods are sold in the market with a label for each functional nutrient. (Table 2)

FOSHU(TOKUHO)and FNFC are now internationally acknowledged as global standards for nutritious functional foods.

From the disease prevention point of view, "Disease Risk Reduction FOSHU" is thought to be the best suited for the purpose of Nutraceuticals. However, the foods which are authorized in this category are only calcium and folic acid at the moment, and so that it is still insufficient to obtain

Table 1 : Food for specified health uses (FOSHU)

Category	Definition of category	Ingredients
FOSHU	The food with labels to displays the function for those who intends to take it for specific purposes in diet.	
FOSHU (disease risk reduction)	Specific Function Food authorized to display a label of disease risk controlled when the risk control ingredient of the food is verified from the viewpoints of medicine and nutrition	Calcium (whish should be specified as an additive in Food Additive Definition etc, and has fully been proved to have the function Folic Acid (PteGlu acid)
FOSHU (Standardized)	Specific Function Food authorized upon evaluation of the compatibility to the standard by Secretariat, without individual evaluation of the Council. This is based on the standard of ingredients which the scientific data has sufficiently accumulated as it is proven to be appropriate as Specific Function Food	Dietary fiber: indigestibility dextrin, polydextrose, guar gum catabolite Oligosaccharide: galacto-oligosaccharide, fructo oligosaccharide, lac ankle oligosaccharide, galacto-oligo glucose, xyleorigo glucose, isomaltooligosaccharide
Limited Conditional FOSHU	Food, not meeting the scientific proof level of effectiveness requirements of Specific Function Food but a certain effectiveness has been verified. It is authorized with conditions as long as it has a label to show the limited function.	

Prepared by the STFC based on Reference[16]

Table 2 : Food with nutrient function claims (FNFC)

	About a system	Nutrient
Food with Nutrient Function Claims	**FNFC** is a food product with labels to show its nutrition. To be a nutrient function food for sale, it is necessary for the food to contain a certain amount of nutrition in the intake per day within the lower/upper limit, as well as to have a notice of its risk.	Zinc, calcium, iron, copper, niacin, pantothenic acid, biotin, vitamin A, β - carotene, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin E, folic acid

Prepared by the STFC based on Reference[16]

effective evidence from the human trials in Japan.

3 Nutraceuticals research in Japan

3-1 Research on analysis and systematization of non-trophic functions of food

As the basic study of food ingredient functions and its roles in Japan, "Research concerning Analysis and Systematization of Non-trophic Functions of Food" (2000-2004) is one of the most advanced examples of Nutraceuticals research in Japan, and it is funded by the Ministry of Education, Culture, Sports, Science and Technology Technical Promoting Adjustment Expense. Professor Soichi Arai of Faculty of Agriculture of Tokyo University and his group made of a scientific evaluation of various non-nutritious ingredients of food, such as flavonoids, carotenoids and peptides, and then created useful databases. This assessment started in 2000. [17](Table 3)

At first, the expected effects of taking functional ingredients, such as anti oxidation, bone formation / absorption, glucose incorporation, influence to immune system, influence to carcinogenic rate of a patient with cirrhosis, liver enzyme induction, learning and biophylaxis factor, were chosen for assessment and verification. However, a big problem which was found out was that sufficient verification was not possible for prevention of diseases such as anti-inflammation action, diabetic control, anti-cancer action and the improvement of the study, because the number of biomarkers, for example, the blood proteins which were proven to have direct effects to prevention of diseases, was too little to judge the overall effects.

During the intermediate stage of the research, it was realized that the attempt to analyze the function of non-nourishment materials in food should not be done by investigating individual biomarkers, but by using a more comprehensive analysis, such as utilizing serum proteome metaborome, which in the future will be able to handle proteins in bulks. This resulted in the conclusion that Nutrigenomics technology needed to be further developed.

Table 3 : Research on analysis and systematization of the non-trophic functions of food

Item	Description
Research on the functions of non-trophic material included in food	1) Extraction/measurement/function assessment of non-trophic material New methodology of functionality and safety, especially introduction of Genomics (Phase 2: to be an independence item from the second stage) 2) Research concerning the amount of flavonoid, and polyphenol, and its function 3) Research concerning the amount and function of terpenoid and carotenoid 4) Research concerning the amount and function of sulfur containing compound, volatile ingredient and spice 5) Research concerning the amount and function of peptides
Research on database of non-trophic material included in food	1) Research concerning non-trophic materials for mutual reaction→ Effectiveness 2) Non-trophic materials integrated database creation/disclosure→ Safety

Source: Reference[17]

Moreover, the effectiveness and safety data obtained through the process above, should be standardized through the examination and evaluation by specialists. It will also need highly reliable evidence, and should be open to public.

In order to discover the new functionality of foods and the importance of scientific proof of effectiveness of functional food ingredients, it is necessary to promptly apply the technique of Nutrigenomics. This database will be the key for the development of Nuraceuticals in the future.

3-2 Cooperative research with industries

Nutraceuticals are food products addressed to public and consumed by ordinal people, therefore, collaboration and technology transfer to various foods and food related companies is essential. It is also thought that the participation of pharmaceutical manufacturers and its affiliated companies, is also essential for advanced evaluations of the effect and safety to the human body. Accordingly, a contribution course by the International Life Sciences Institute, ILSI "Functional food genomics" (Functional Food Science and Nutrigenomics) was founded by The University of Tokyo graduate school Agricultural Life Science Research Course, for the aspects of industrialization and practical use of Nutraceuticals for the period of December, 2002 to November, 2008.

Thirty-two food companies are participating in this program, as well as industry-academia projects led by Professor Keiko Abe. Specifically, each company is trying to examine the variation and clarify the function of the gene expression level by the intake of food elements, such as proteins and amino acids, which they are interested in developing They have also started to create a shared database linked with the gene expressions obtained from food functions and DNA chips. [18] The industry-academia projects have gained a lot of attentions globally, as it is aimed at thoroughly evaluating the overall function and safety of food and food ingredients, and assuring the foundation for quality design and quality control.

3-3 Scientific evaluation in human

It is essential to obtain data of disease prevention, by showing the effectiveness in human for developing Nutraceuticals. In order to achieve this, it is necessary to prepare teams similar to pharmaceutical development, such as selection of biomarkers and end point, creation of the standard protocols for the examination, recruitment of appropriate examinees, and objective evaluation by medical doctors. Unfortunately, it is notable that Japan is lags behind other countries in terms of Nutraceuticals development.

Professor Toshikazu Yoshikawa of the Department of Medicine at Kyoto Prefectural University Professor Soichi Arai of Tokyo University of Agriculture and others are taking the lead to establish the "Society for the Function of Food and Exercise",which was established in 2006. The purposes of this association are to study the relationship between food and medical functions by advanced technologies, to develop new functional foods which contribute to health maintenance for people and to develop physical programs suitable for various age and health conditions. A cluster system for industrial development will be created based on the above activities. Specifically, this is to create a database by using Nutrigenomics, for example, by collecting information about the scientific effectiveness using biomarkers related to food.(Table 4)

The "Society of Functionality Research of Food and Movement" started to acquire scientific data of functional foods on human body by collecting various functional foods from the industry in 2007. This is an activity to analyze the potential of foods by medical doctors and academic researchers. They received 15 entries and 5 items (5 companies) were selected for further assessment. Currently, it is scheduled to form 5 assessment teams, in collaboration with Japan Physicians Association, to create specific assessment programs and tests for scientific evidence using volunteers in 2008.[20] In addition, the "Healthy Food Material Evaluation Committee" has been formed, based on the achievement of the projects, for the research and development, evaluation, and creation of the information systems.

4 Nutraceuticals research in Europe

In Europe, many countries such as the Netherlands, France, Germany, Belgium and Spain place emphasis on agriculture. Above all, in the Netherlands, dairy products and beer have a long history of food processing / fermentation technology, which makes this country one of the prominent food industry countries in Europe. For example, the amount of exported farm products such as meat, dairy products, grain, seed, food and beverage products, and tobacco and its processed products, is in second place in the world.[21] Above all, dairy products and beer are tops in the world.

The Netherlands is competitive in regards to advanced technologies, as they have a wide range of knowledge, know-how, experiences, and supports, from basic research to industrialization for processing and fermentation technologies for foods, dairy products, and beer.[21] In the Netherlands, "Food Valley" is the largest scale food products cluster in Wageningen. The Nutrigenomics Institute of the nourishment genome research center in Europe also works in this city. This is a place for research for the European food industry. This document introduces examples of the Nutraceuticals research and development in Europe, referring to the case studies of the Netherlands.

4-1 Food valley in the Netherlands

The Agriculture Ministry of the Netherlands integrated the Wageningen Agricultural University and Institute of Technology of Agricultural Ministry, to establish Wageningen University (Wageningen UR: Wageningen University and Research Center) in 1988, for focusing on the research and development of food. [22] On the other hand, Wageningen Center for Food Science was established in 1997 by Ministry of Economic Affairs in Wageningen as a center of activation for the food industry. [23] Both organizations are strongly supported by the government of the Netherlands.

When Wageningen University and Wageningen Nutrition Center were established, a strong research infrastructure for the application was formed concerning food in this country. In addition to this, the organizations supporting industrialization and technological transfers such as TNO Nutrition & Food Research and NIZO Food Research made a partnership, therefore, the technological transfer and industrialization of advanced technologies have been conducted continuously. Afterwards, many food companies have come to the city to create Food Valley, thus, enterprises, administration and technical institutes could work in cooperation

Table 4 : Purpose and research items of society of functionality research of food and movement

Purpose	New industries are to be created through collection and database of various information of scientific evidences concerning the physiological function and the health care related to food (especially, functional food materials) by making best use of advanced technologies (genomics, proteomics, and metabolomics)
Contents of research	1) Research of functionality and safety of side goods involved in human health 2) Clarification of fundamental molecular mechanism concerning health care and disease prevention of food and ingredients 3) Research concerning the relationship between nutrition intake and health associated with genes 4) Development and application of the biomarkers to clarify functionality and risk 5) Scientific elucidation of health care by exercise and establishment of individual exercise menu 6) Evaluation and development of health care and exercise supporting tool

Source: Reference[19]

Table 5 : Various organizations in food valley and its function

University, laboratory, and research institutes in Food Valley	Role and function
Wageningen University & Research Centre: - Wageningen Institute for Food Safety [27] - Agrotechnology and Food Science Group [28] - Plant Research International Wageningen [29] - Animal Sciences Group - Wageningen Institute for Food Law	Basic and fundamental research A part of European Nutorigenomics Organization (NuGO) Basic research of science of food Plant improvement using the genomics technology. Animal test research
TNO Food & Nutrition [30]	Technological transfer of basic research results to enterprises, commitment of researches for enterprises
NIZO Food Research (NIZO)[31]	Technological transfer of basic research results to enterprises, commitment of researches for enterprises
Center for BioSystems Genomics[32]	Consortium composed of several ten enterprises, including Warheningen UR to play a key role. For improvement of quality and nature of grains by using Nutorigenomics technology.
Nutrigenomics Consortium [33]	Research of biomarkers using Nutorigenomics technology, focusing on diabetic, hyperlipemia, and high blood pressure resulted from the Metabolic syndrome.
Top Institute Food and Nutrition [34]	Technical assistance necessary to provide new food products that contribute to health

Prepared by the STFC based on Reference[27-34]

to make the largest food research and development cluster in Europe. Thus, this city became a place of innovation for new food companies. [24-26](Table 5)

4-2 TNO nutrition & food research

TNO of the Netherlands is the largest general contracting institution in Europe, and was established in 1932 for application studies in the science and technology fields. The total number of staff is more than 5,000. The five research areas cover: (1) Quality of Life, (2) Defense and Public Safety, (3) Natural and Built Environment, (4) Advanced Products, (5) Process Systems and (6) ICT and Services. Amongst these, the Quality of Life department is working on nourishing food products, mainly for technology transfers upon contract with industrial companies. In particular, applicability and toxicity tests are conducted for nourishing food products. They provide assessment services for new food product safety, the applicability for functional foods. In addition, they submit the necessary paperworks for registration and application to the European Food Safety Authority: EFSA and American Food and Drug Administration: FDA. [30]

Above all, it is notable that they have expertise in the tests for functional foods and new food products on human volunteers. They have many achievements in human volunteer tests of functional foods, as they have the evaluation and analytical technologies for various in-body markers, and human metabolism test facilities. Along with this, the nourishment database is further fulfilled with their vast database. Several thousands of volunteer databases are available for the testing of various new food products, which will provide a smooth launching and operation for new tests. (Table 6)

4-3 NIZO food research BV

The NIZO Food Research Facility, for contracting with enterprises on research activities, is located in Ede city near Wageningen. NIZO has food related laboratories and the pilot plants for the testing of food production. Clients inquire to them to conduct various tests for production before the full investment of a production facilities. Thus the companies can have business supports from NIZO just before the production. [31,36]

4-4 NuGO; European nutrigenomics organization

When Nutrigenomics was established as new nourishment genomic technologies for development of Nutraceuticals, the European Nutrigenomics Organization was founded with the members of 22 organizations from 10 countries in Wageningen in January 2004. This location became the center of the food science in Europe for (1) education of post genomic science, that is, Nutrigenomics technology' (2) promotion and integration of

Table 6 : TNO commitments and services for testing and research

Committed test and registration services[1]	Consulting investigation concerning regulations 1) Confirmation of applicable regulations 2) Confirmation of required data 3) Pre-assessment of customer data 4) Proposal of cost
Committed test and registration services[2]	1) Evaluation of data 2) Safety testing 3) Preparation of application forms
Other services	·Examination of human volunteer - Test design · Enterobacteria/immunization test - Allergic examination ·Various analyses of nourishment, chemical substances, and microorganisms ·Nourishment evaluation and nourishment genomics ·The biomarker's identification - Epidemiology examination
All processes from the regulation investigation to the application	·Research on laws and regulations – Implementation of toxic test · Preparation of application forms

Source: Reference[35]

Nutrigenomics technologies for contribution to nourishment science in Europe, (3) application and industrialization of Nutrigenomics technology from the global aspects and (4) establishment of the advanced virtual center of the Nutrigenomics technology. [37]

Currently, 23 organizations (university and enterprise) participate in the projects as partner organizations, for not only for the research but also for the promotion of the industrialization. The technologies in which NuGO is specialized, is the creation of the database for bioinformatics (Nutrientgene database), concerning the ingredients of foods and its function and physiological activities. This is done by making good use of a genomic technologies and microarray technologies. This database is designed, from the beginning, to be shared for practical use. The data format is common for NuGO participants. Moreover, the research protocols for data acquisition are also standardized in a common format, which is effective for the faultless and prompt process from academy to industry. [28] The databases are currently available to be shared by the participants. The standards and formats that NuGO are promoting may be used not only in Europe, but also as the global standard in the future.

5 Nutraceuticals research in the United States

In Europe, a focus is placed on a faultless approach, from research to industrialization, of Nutraceuticals, mainly promoted in Food Valley. On the contrary, the United States is focusing on the approaches for prevention of diseases and life-style related diseases based on the study of Nutraceuticals. Some venture companies are now working a service to provide Nutraceuticals for those who easily contract diseases, through individual genetic information analysis.

5-1 UC Davis : disease prevention

It has been acknowledged that Nutrigenomics technology is effective for identifying the relationship of food ingredients and physiology. The Center of Excellence for Nutritional Genomics was established by UC Davis (University of California, Davis) in 2004 in the United States, backed by the funds of NIH, coinciding with the establishment of the NuGO (mentioned above) in Europe.

Dr. Rodriguez of UC Davis has been engaged in the administration of the research. His philosophy is that now is the time to shift the mindset concerning medicine, from remedy of sickness to pursuing health and wellness. In other words, it should be shifted from medication to prevention. This is because of the increase of life-style related diseases resulting from bad eating habits and lack of exercise becoming a social issue. Foods should play a key role for prevention of diseases, so that Nutrigenomics technologies are effective for development of functional foods of Nutraceuticals. [39] For instance, research is conducted mainly for bioactive substances contained in plants, such as food herbs, to identify relationships of foods and gene expression, or medical treatment and preventative medicine. The nonlinearity algorithm called an Isomap is used to process a large number

of genetic information about a biomarker, by using microchip technologies. The examination has been progressed.

5-2 Tufts University: clinical research of disease prevention

Tufts University has the Human Nutrition Research Center on Aging (HNRCA). Professor Schaefer offers a low fat diet to volunteer examinees, who live in the outskirts of Boston, for monitoring their health status, and to test and research various disease prevention measures such as for obesity, diabetic and heart failures. They have hospital-level clinical laboratories, kitchen facilities for special diets and counseling rooms in the university for various functions, from processing/cooking of functional foods, to the guidance/consulting of the examinees. Tens of volunteer examinees are participating in each project.

For example, the saccharified albumin (Glucose-attached Albumin), generated by obesity and in a diabetic process, is used as one of the biomarkers to create databases to identify relationships between low fat diet and obesity, diabetes mellitus, or renal diseases, as well as for any results to control the risk of such diseases. This research and test also aims to encourage the examinee themselves to improve their eating habits for successful results.

5-3 Venture companies

Some venture companies have already been working on launching the business based on this technology in the United States, where it is common for venture companies to involve in industrialization of research results. Sciona Inc,[41] in Colorado provides services to diagnose personal genes and identify whether they are prone to contracting diseases. For example, they examine the SNP (personal genetic information) profiles of 19 disease-related genes. Based on the medical data (current health condition) and questionnaire (lifestyle information, they consult with the customers on how they can change their dietary habits and life styles.

The NutraGemomincs Inc, in Chicago started a business to support the development of Nutraceuticals foods effective for disease prevention, as well as the gene-based pharmaceutical development, by providing a test system to identify genes affected by dietary habits or gene type. Although these businesses have just started and their results will come later, it is expected to contribute to the acceleration of the movement to shift academic results to practical application.

6 Future issues and proposals

For diseases expected to increase in number, but can be prevented by lifestyle change, such as metabolic syndromes, the patients are required to positively change their lifestyles. One of the solutions is to change their diet. Nutraceuticals should contribute to prevention of such diseases. For Nutraceuticals,there are three key issues of the technology: (1) establishment of scientific assessment standard for prevention of diseases, (2) establishment of assessment system for disease prevention by human trials and (3) establishment of seamless system to transfer stage from basic research to industrialization. The following is a proposal for Japan to approach research trends in this area from a global viewpoint.

6-1 Establishment of scientific assessment standard for prevention of diseases

Medicines are created from a single ingredient. As the target molecule on which the ingredient would directly act is basically a single material, an assessment for drugs, even for the same disease, will be made for each medicine or target molecule in general.

On the other hand, Nutraceuticals are not necessarily a single material, therefore, the expected effect for disease prevention may be activated by a complex action by plural materials. For the example of prevention of diabetes, it is necessary to demonstrate that plural composition materials contained in food have a preventative effect against diseases by exerting the effects on some paths which trigger the disease. It is also necessary to compare preventative effects for different types of food. Therefore, it is necessary to select multiple indicators (biomarkers) to determine prevention effects of diabetes, and to standardize the assessment method. In other words, it is urgently necessary to conduct biomarker research

for prevention of target diseases.

This issue has been pointed out by Professor Soichi Araki, that the number of biomarkers is too little to achieve general functionality, as reported in "Analysis of Non-nourishment Materials in Food and Research on Systematization" in 2000-2004. In the past studies of medicine, biomarkers for medical treatment were actively studied, while it was the time to promote the research of biomarkers for disease prevention by Nutraceuticals. Data obtained with a separate evaluation protocol by different technical institutions are inconsistent. It is difficult to make an appropriate evaluation without common data. Therefore, it is also necessary to define the measurement method of biomarkers and standardize indicators.

Furthermore, the database concerning disease prevention for Japanese people is an invaluable asset of Japan, and so it is meaningful to share with many research and development institutions. It is thought to be necessary to create a uniform format, from the basic research phase, to share the database of food ingredients and disease prevention effects.

6-2 Establishment of assessment system for disease prevention by human trials

Examinations using food and food ingredients were not conducted in a systematic manner to prove the effectiveness of disease prevention for humans. It is now necessary to establish a system to provide scientific assessment of this subject. This is the key issue to creating Nutraceuticals.

As described earlier in the example of Tufts University in the United States, they have a team consisting of medical doctors, dietitians, and physiologists, to work on the research of food for disease prevention with volunteer examinees. In Europe, the food research and development base called Food Valley has assessment systems which are making full use of Nutrigenomics technologies by TNO, which commits itself to the identification of materials and demonstration tests of efficiency for humans.

Human-based systematic examination has just started in Japan. Professor Toshiichi Yoshikawa and Professor Soichi Arai launched the "Society for Function of Food and Exercise" to start the evaluation within humans, as mentioned above. This activity is expected to propose elements required for human-based research, assessment, and know-how of its operation. In Japan, there are many good cooking materials to contribute to our health, as brought up in the enriched history. A systematic and general research concerning identification of effective ingredients and disease prevention has just started.

Therefore, it is urgently necessary to create a center like Food Valley for researchers, doctors, diagnosis/assessment researchers and enterprises to provide food materials, in order to create superior Nutraceuticals from Japan-made cooking materials, as well as fulfillment of a general evaluation system.

6-3 Establishment of seamless system to transfer stage from basic research to industrialization

Nutrigenomics, which have been rapidly innovated in this century, keeps upgrading itself as basic technologies to create Nutraceuticals. It is also applied to practical approaches for evaluation of Nutraceuticals. At the same time, its advancement continues as a fundamental research. Therefore, it is worth noting that the sites of research and application are very close to each other. The case study of Wageningen in Europe is a good example to show how the seamless cooperative system functions well to support various basic researches, application of enterprises and practical approaches. The important points for this "seamless" cooperative system are: Firstly, a cooperation of research beyond the border of academia such as science, agriculture, fishery study, engineering, pharmacology and medicine, in other words horizontal link of areas. Secondly, a support system to shift the basic research results, to industrialization in relation to the development of parties concerned, to expedite its commercialization, or vertical linking.

For horizontal links, Nutrigenomics technology itself is a composite technology of basic research, an integrated research team under the keyword Nutrigenomics should be established in an environment like Food Valley, as described in 6-2.

On the other hand, for vertical linking of areas, it is still hard to create a support organization to commit research and development by bridging the basic research area (academia) and enterprises, to

facilitate the industrial transfer in Japan. Although it is thought that venture capitals are taking the rope to function in the United States, it might be rather difficult model for Japan, where the venture companies are still immature. It seems that support organizations such as TNO and NIZO in Europe are good examples to study.

7 Conclusions

It is the wish of all people to live healthy. It is natural that people's focus is shifting from medical treatment for sickness to a positive approach for prevention of diseases to stay healthy. In order to prevent diseases and be healthy, new food products, which have been proven by the human trials to be effective to prevent diseases, should gradually penetrate into the society. This will improve QOL (quality of life) of all people.

Nutraceuticals is a scientific area generated from Japan to the world. It can be said that Japan created a brand-new conception of food. In order to develop this movement, not only for the improvement of scientific research levels, but also for the improvement of the quality of life by utilization, it is required to note the following three actions: (1) establishment of scientific assessment standard for prevention of diseases, (2) establishment of assessment system for disease prevention by human trials and (3) establishment of seamless system to transfer stage from basic research to industrialization.

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